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<p>(21) International Application Number: PCT/US97/19230</p> <p>(22) International Filing Date: 27 October 1997 (27.10.97)</p> <p>(30) Priority Data: 60/029,348 31 October 1996 (31.10.96) US 9624375.3 22 November 1996 (22.11.96) GB</p> <p>(71) Applicant (<i>for all designated States except US</i>): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): BELL, Ian, M. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GUARE, James, P., Jr. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HAZUDA, Daria, Jean [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MUNSON, Peter, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). THOMPSON, Wayne, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VACCA, Joseph, P. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: BENZODIAZEPINE HYDRAZIDE DERIVATIVES AS INHIBITORS OF HIV INTEGRASE</p> <p>(57) Abstract</p> <p>Compounds having a benzodiazepine hydrazide core are described. These compounds are useful in the inhibition of HIV integrase, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.</p>			

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TITLE OF THE INVENTION
BENZODIAZEPINE HYDRAZIDE DERIVATIVES AS
INHIBITORS OF HIV INTEGRASE

5 BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid cells. Integration is believed to occur in three stages: cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site; repair synthesis by host enzymes.

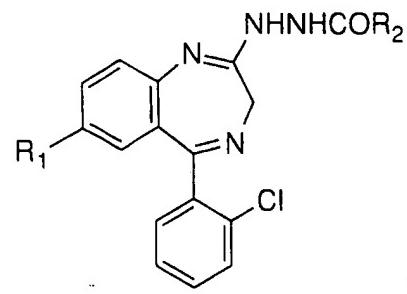
Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. *et al.*, *Nature*, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an integrase and an HIV protease [Toh, H. *et al.*, *EMBO J.* 4, 1267 (1985); Power, M.D. *et al.*, *Science*, 231, 1567 (1986); Pearl, L.H. *et al.*, *Nature*, 329, 351 (1987)].

It is known that some antiviral compounds act as inhibitors of HIV and are effective agents in the treatment of AIDS and similar diseases, e.g., azidothymidine or AZT. Applicants demonstrate that the compounds of this invention are inhibitors of HIV integrase, probably by inhibiting catalysis rather than preventing assembly. The particular advantage of the present invention is highly specific inhibition of HIV integrase. The compounds of the present do not inhibit a variety of other protein-nucleic acid interactions, including enzymatic reactions involving

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HIV reverse transcriptase, DNase I, Eco RI endonuclease, or mammalian polymerase II, as well as other related interactions, e.g., involving HIV TAT protein.

Vejdelek et al., "Potential Anxiolytics and Hypnotics: 1-
5 (Alkanesulfonamidoalkyl)-6-aryl-8-halogeno-s-triazolo[4,3-a]-1,4-
benzodiazepines and related compounds," Collection Czechoslovak
Chem. Commun. 53:132-144 (1987), describe the following
compounds of structural formula IA:

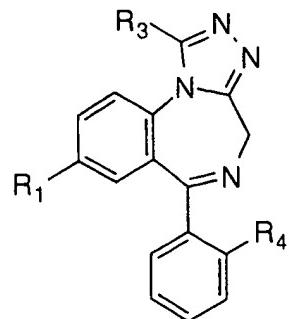


Compound	R ₁	R ₂
1	Cl	
2	Br	
3	Cl	

10

as useful intermediates in making the psychoactive drugs of structural formula IIA:

- 3 -



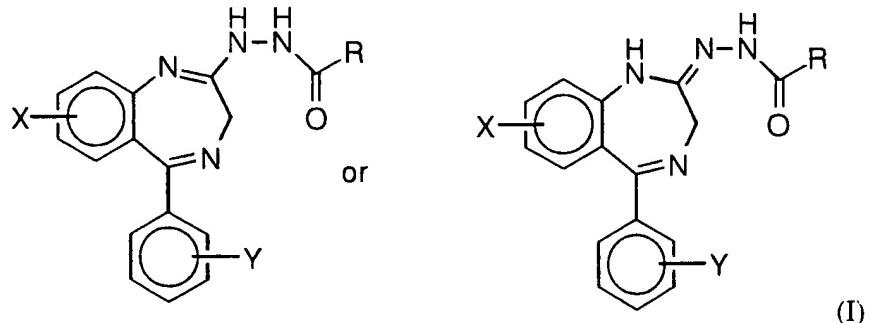
BRIEF DESCRIPTION OF THE INVENTION

Compounds of formula I, as herein defined, are disclosed. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts or hydrates (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

15 DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with compounds of formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV integrase, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). Compounds of formula I are tautomers defined as follows:

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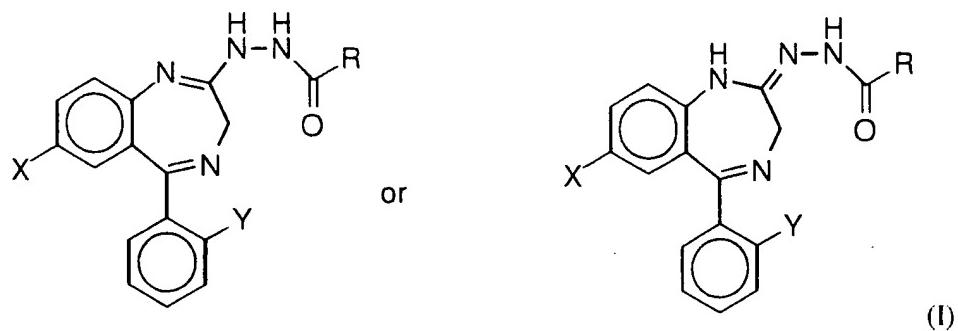


wherein X and Y are independently H, Cl, Br or F;

- 5 R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4 alkoxy, halo, nitro, phenyl or halophenyl,
provided that:
(a) R is not 4-cinnolinyl, and
- 10 (b) when R is 5-methyl-4-imidazolyl, X is H or F;
or pharmaceutically acceptable salts thereof.

In one embodiment of the present invention is directed to the tautomers of structural formula I,

15



wherein X and Y are independently H, Cl or Br;

- 5 -

R is aryl or heterocycle, either of which is unsubstituted or substituted with C₁-4 alkyl, or C₁-4 alkoxy,

provided that:

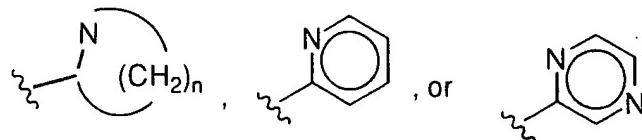
when R is 5-methyl-4-imidazolyl, X is H;

5 or pharmaceutically acceptable salts thereof.

In one class of this embodiment, X and Y are independently H, Cl, or Br;

R is

10



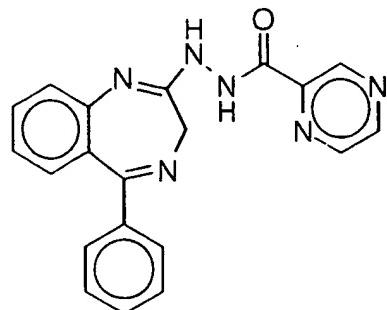
wherein R is unsubstituted or substituted with one or more of C₁-4 alkyl; nitro; C₁-4 alkoxy or halo-C₁-4 alkyl,
n is 3 to 6,
or a pharmaceutically acceptable salt thereof.

15

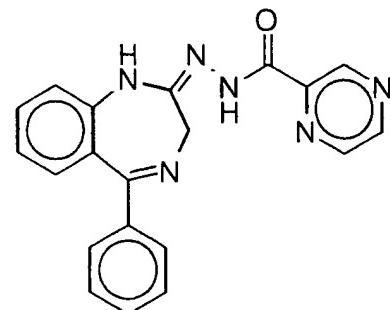
A particular subclass of this class is directed to tautomers of structural formula (I) wherein: X and Y are hydrogen; R is aryl, pyrazinyl, pyridyl, imidazolyl, pyrimidinyl, quinolinyl, any of which R substituents are unsubstituted or substituted with C₁-4 alkyl, or pharmaceutically acceptable salts thereof.

20

Particular examples of compounds of the present invention are:



and



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and pharmaceutically acceptable salts thereof.

The present invention further relates to a method of inhibiting HIV integrase comprising administering to a mammal, most particularly a human, an effective amount of a compound of formula (I).

The present invention also has as an object the method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC in subject in need of such treatment, comprising administering to the mammal, most particularly a human, an effective amount of a compound of structural formula (I).

Yet another object of the present invention is to provide pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

The present invention also relates to the use of a compound of structural formula (I) for the preparation of a medicament useful for the treating infection by HIV, or of treating AIDS or ARC in a subject in need of such treatment, and for prevention infection of HIV in an exposed subject.

The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as racemates, racemic mixtures or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., R, etc.) occurs more than one time in any constituent or in formula I, its definition at each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. "Halogen" or "halo" as used herein, means fluoro, chloro, bromo and iodo.

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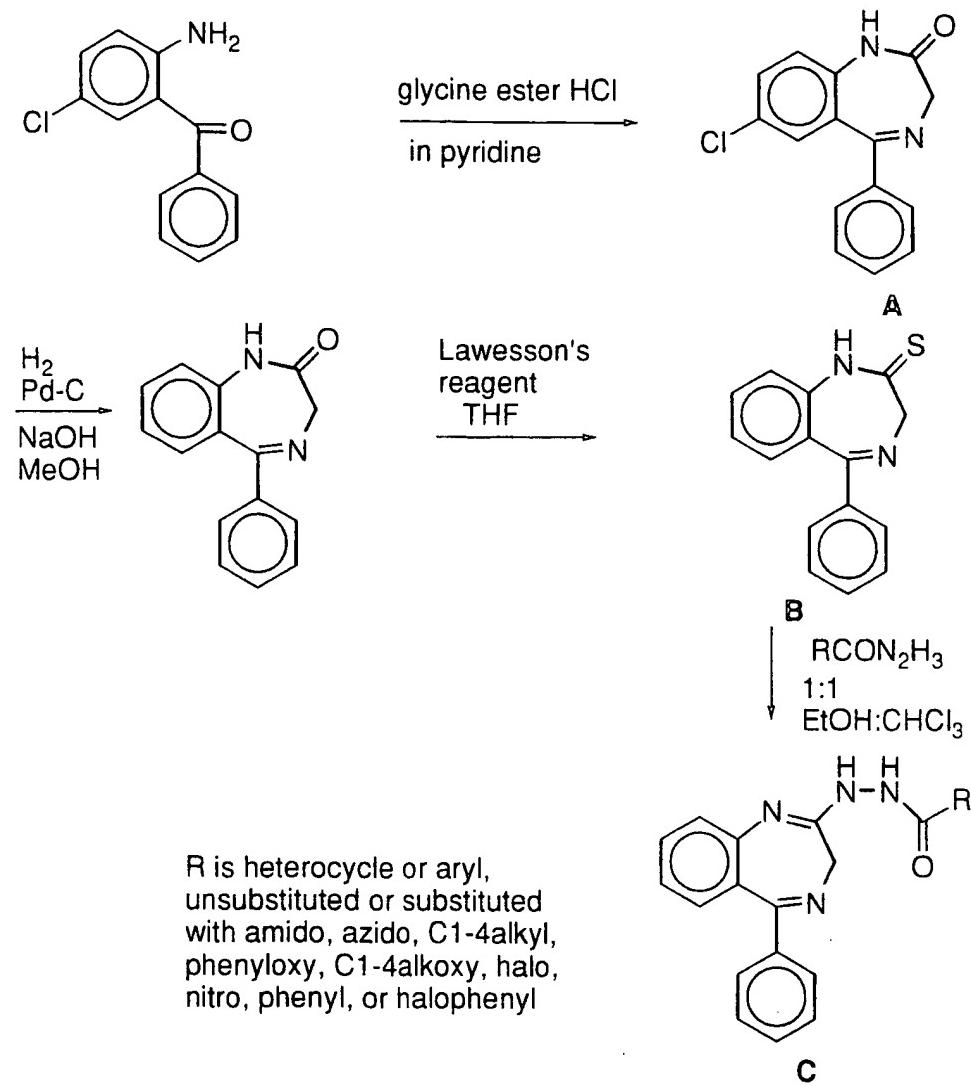
As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl.

- The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or 5 stable 7- to 10-membered bicyclic heterocyclic ring system, any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom 10 may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.
- Examples of such heterocyclic elements include piperidinyl, piperazinyl, 15 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, 20 quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoazazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl.
- 25 The pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 30 diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide. These salts may be prepared by standard procedures, e.g. by reacting the free acid with a suitable organic or inorganic base.

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The compounds of the present invention can be synthesized by the following Schemes.

SCHEME I

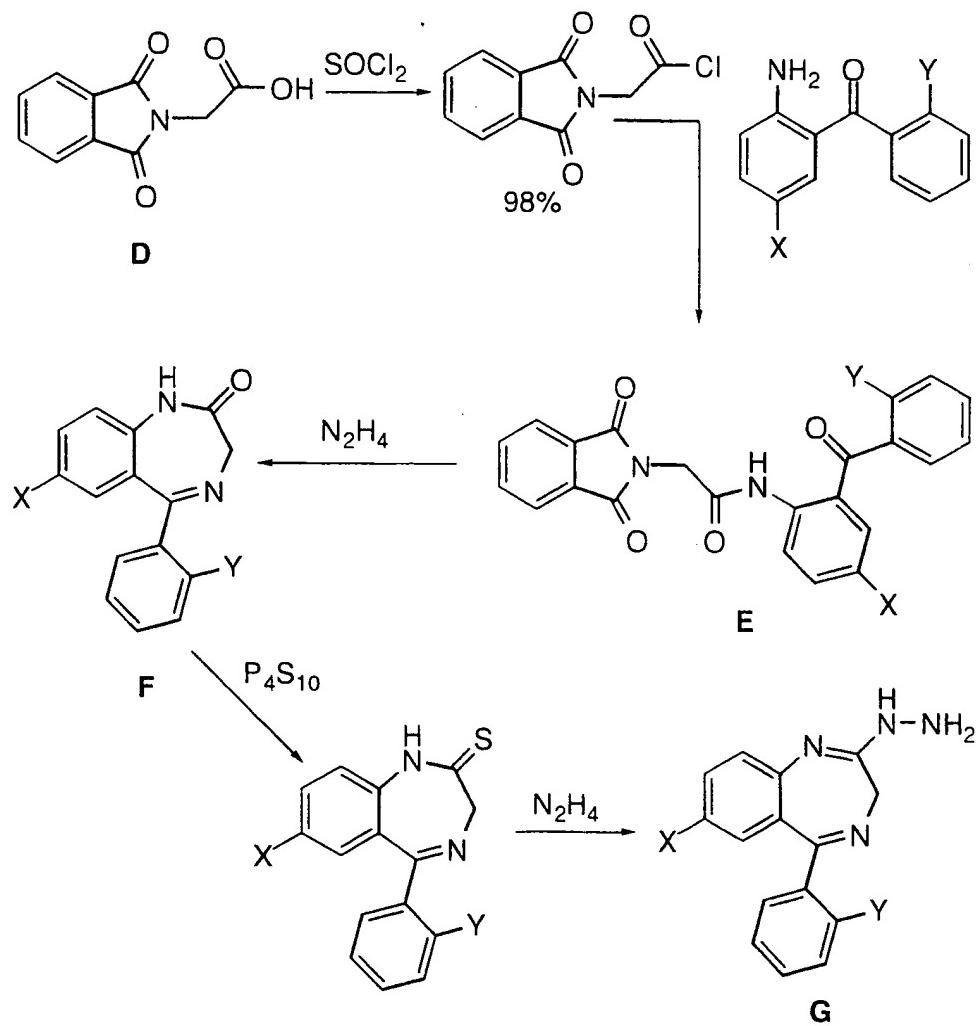


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In Scheme 1, 2-amino-5-chlorobenzophenone is reacted with glycine esters to give A. Thiation is carried out by subsequent reaction with Lawesson's reagent, which upon further reaction with RCON₂H₃, affords compounds of formula C of the present invention.

5 See also Sternbach, L.H., *et al.*, *J. Org. Chem.* 27, 3788(1962).

SCHEME II



X is H, Cl, Br or F.

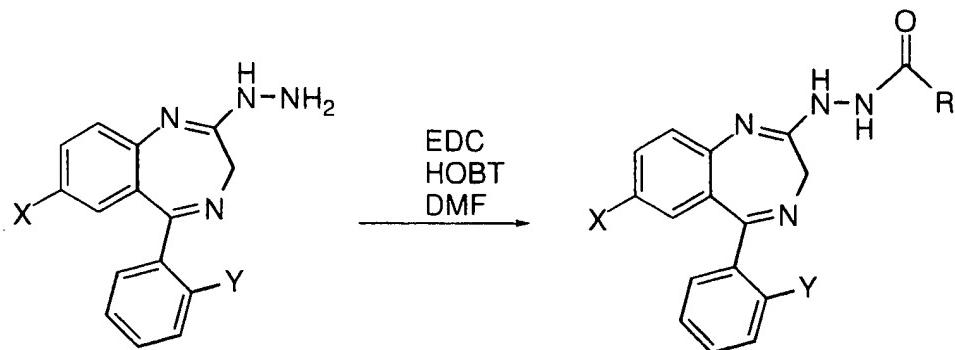
Y is H, Cl, Br or F.

- 10 -

Scheme II illustrates another way to build benzodiazepine hydrazides of the present invention. N-Phthaloylglycine **D** is converted to its acid chloride, then reacted with 2-amino-5-substituted benzophenone to give **E**. See also Vejdelek, Z., et al., *Coll. Czech. Chem. Commun.* 45, 3593(1980). Reaction with hydrazine gives the benzodiazep-2-one **F**, which is then subjected to thiation. A further step with hydrazine gives **G**, another set of compounds of the present invention.

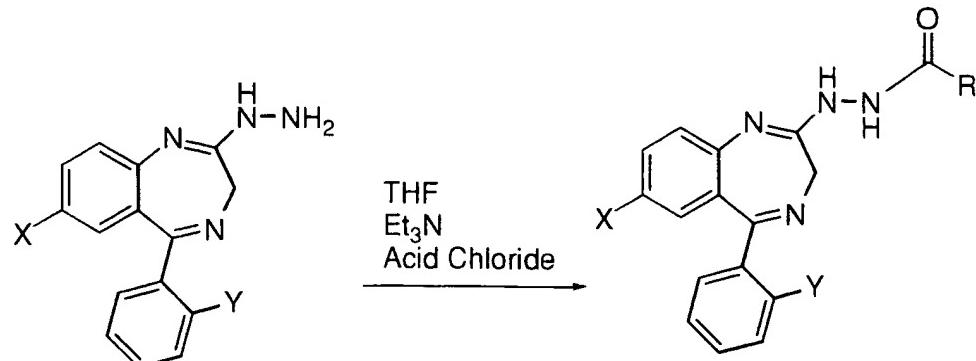
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SCHEME III



R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4
15 alkoxy, halo, nitro, phenyl or halophenyl.

SCHEME IV



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R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4 alkoxy, halo, nitro, phenyl or halophenyl.

5 Schemes III and IV illustrate how to derivatize the hydrazide group by either EDC (1-(3-dimethylamionopropyl)-3-ethylcarbodiimide hydrochloride) -mediated coupling to a carboxylic acid or direct acylation with an acid chloride.

10 The compounds of the present inventions are useful in the inhibition of HIV integrase, treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited
15 to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, exchange of body
20 fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

25 The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are
30 commercial products to be sold for these purposes.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in

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dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the
5 invention or a prodrug of a compound of the invention to the individual in need of treatment.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment
10 involves administering to a patient in need of such treatment a therapeutically-effective amount of a compound of the present invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the
15 specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The present invention also has the objective of providing suitable systemic, oral, parenteral and topical pharmaceutical
20 formulations for use in the methods of treatment of the present invention. The compositions containing the compound of the present invention for use in the treatment of the above-noted hyperandrogenic conditions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration. For
25 example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form,
30 all using forms well known to those of ordinary skill in the pharmaceutical arts. The compositions may also be administered as a nasal spray or as a suppository.

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- When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.
- When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

- The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

- When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

- The compounds of this invention can be administered orally to humans in a dosage range of 1 to 1000 mg/kg body weight in single or divided doses. One preferred dosage range is 0.1 to 200 mg/kg body weight orally in single or divided doses. Another preferred dosage range is 1.0 to 100 mg/kg body weight orally in

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- single or divided doses. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0,
- 5 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including
- 10 the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.
- 15 The present invention is also directed to combinations of the HIV integrase inhibitor compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following table. The term "administration" refers to both concurrent and sequential administration of the active agents.
- 20

25

TABLE

ANTIVIRALS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC

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Acemannan	Carrington Labs (Irving, TX)	ARC (See also immunomodulators)
Cytovene Ganciclovir	Syntex (Palo Alto, CA)	sight threatening CMV peripheral CMV retinitis
d4T Didehydrodeoxy- thymidine	Bristol-Myers (New York, NY)	AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers (New York, NY)	AIDS, ARC
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (See also immuno- modulators)

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<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Trisodium Phosphonoformate	Astra Pharm. Products, Inc. (Westborough, MA)	CMV retinitis, HIV infection, other CMV infections
Dideoxycytidine; ddC	Hoffman-La Roche (Nutley, NJ)	AIDS, ARC
Novapren	Novaferon Labs, Inc. (Akron, OH) Diapren, Inc. (Roseville, MN, marketer)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Zidovudine; AZT	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv, ARC pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV disease, neuro- logical involvement, in combination with other therapies.

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<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
Alpha Interferon	Burroughs Wellcome (Rsch. Triangle Park, NC)	Kaposi's sarcoma, HIV in combination w/Retrovir
Acyclovir	Burroughs Wellcome	AIDS, ARC, asymptomatic HIV positive, in combination with AZT.
Antibody which neutralizes pH labile alpha aber- rant Interferon in an immuno- adsorption column	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC

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Indinavir	Merck & Co., Inc. Rahway, NJ	AIDS, ARC, pediatric AIDS (protease inhibitor)
Lamivudine (3TC)	Glaxo Wellcome (Rsch. Triangle Park, NC)	AIDS, ARC (protease inhibitor)
Nevirapine	Boehringer Ingleheim	AIDS, ARC (protease inhibitor)
Delavirdine	Pharmacia-Upjohn	AIDS, ARC (protease inhibitor)
Ritonavir	Abbott	AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	AIDS, ARC (protease inhibitor)
Nelfinavir	Agouron Pharmaceuticals	AIDS, ARC (protease inhibitor)
141 W94	Glaxo-Wellcome	AIDS, ARC (protease inhibitor)
DMP-266	DuPont-Merck Pharmaceuticals	AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)

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IMMUNO-MODULATORS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AS-101	Wyeth-Ayerst Labs. (Philadelphia, PA)	AIDS
Bropirimine	Upjohn (Kalamazoo, MI)	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC (See also anti-virals)
CL246,738	American Cyanamid (Pearl River, NY) Lederle Labs (Wayne, NJ)	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (See also anti-virals)
Gamma Interferon	Genentech (S. San Francisco, CA)	ARC, in combina- tion w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute (Cambridge, MA) Sandoz (East Hanover, NJ)	AIDS

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<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel (Somerville, NJ) Immunex (Seattle, WA)	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough (Madison, NJ)	AIDS
		AIDS, in combina- tion w/AZT
HIV Core Particle Immunostimulant	Rorer (Ft. Washington, PA)	seropositive HIV
IL-2 Interleukin-2	Cetus (Emeryville, CA)	AIDS, in combina- tion w/AZT
IL-2 Interleukin-2	Hoffman-La Roche (Nutley, NJ) Immunex	AIDS, ARC, HIV, in combination w/AZT
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL

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<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Imuthiol Diethyl Dithio Carbamate	Merieux Institute (Miami, FL)	AIDS, ARC
Alpha-2 Interferon	Schering Plough (Madison, NJ)	Kaposi's sarcoma w/AZT: AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp. (Summit, NJ)	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen (Thousand Oaks, CA)	AIDS, in combination w/AZT
rCD4 Recombinant Soluble Human CD4	Genentech (S. San Francisco, CA)	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen (Cambridge, MA)	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche (Nutley, NJ)	Kaposi's sarcoma AIDS, ARC, in combination w/AZT

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<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
SK&F106528 Soluble T4	Smith, Kline & French Laboratories (Philadelphia, PA)	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech (S. San Francisco, CA)	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Clindamycin with Primaquine	Upjohn (Kalamazoo, MI)	PCP
Fluconazole	Pfizer (New York, NY)	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp. (Princeton, NJ)	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow (Cincinnati, OH)	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment

- 23 -

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Piritrexim	Burroughs Wellcome (Rsch. Triangle Park, NC)	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation (Bedford, MA)	PCP prophylaxis
Spiramycin	Rhone-Poulenc Pharmaceuticals (Princeton, NJ)	cryptosporidial diarrhea
Intraconazole- R51211	Janssen Pharm. (Piscataway, NJ)	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Recombinant Human Erythropoietin	Ortho Pharm. Corp. (Raritan, NJ)	severe anemia assoc. with AZT therapy
Megestrol Acetate	Bristol-Myers (New York, NY)	treatment of anorexia assoc. w/AIDS
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals (Norwich, NY)	diarrhea and malabsorption related to AIDS

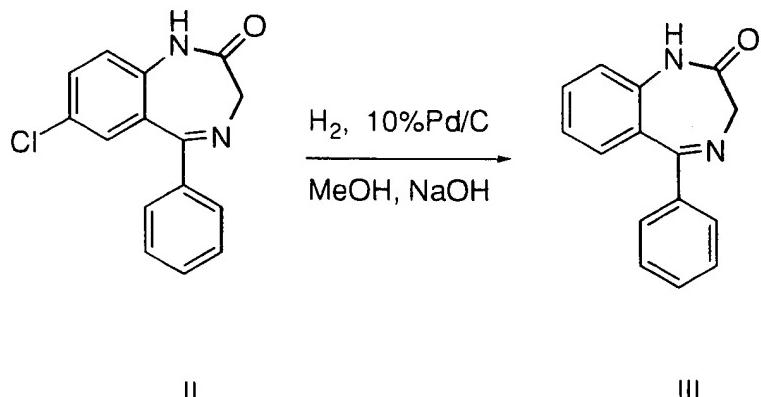
It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immuno-modulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any

- 5 pharmaceutical composition useful for the treatment of AIDS.
Indinavir is an inhibitor of HIV protease and is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate. Its synthesis is set forth in
10 U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day.

EXAMPLE 1

Step I Preparation of Compound III

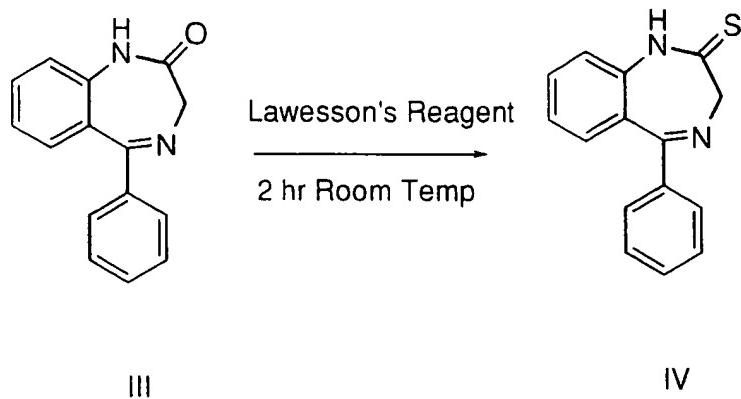
15



A Parr-bottle was charged with 0.074 g (1.85 mmol) of solid NaOH, 20 mL of dry methanol, 0.500 g (1.85 mol) of compound II, and 0.050 g of 10% Pd on carbon. The Parr-bottle was placed onto the hydrogenation apparatus, charged with hydrogen at 42 psi, shaken for 2 hrs 20 min., and the contents were filtered through a plug of Celite™ diatomaceous earth which was washed with 50 mLs of EtOAc. The organic layer was collected and then concentrated on a rotovap to afford an oil which was triturated with EtOAc/hexane to give solid product III.

- 25 -

Step II Preparation of Compound IV



5

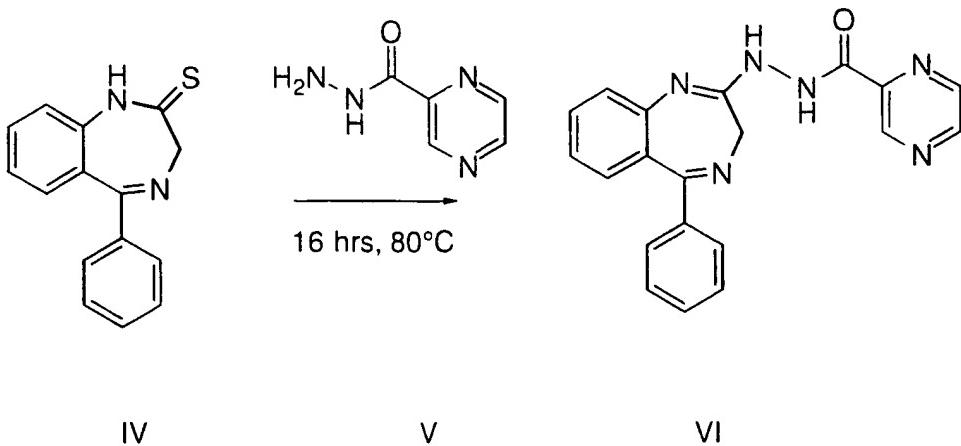
Ref: Tetrahedron 40, 2047-2052, 1984.

A 100 mL round bottom flask was charged with 1.0 g of II, the product from Step I, 50 mL of dry THF, and 0.820 g of Lawesson's reagent. The reaction was allowed to stir for 2 hrs at r.t. The reaction was concentrated to give an oily residue which was chromatographed with 3:1 EtOAc/hexane. The fractions containing product were concentrated and the residual solid was recrystallized using EtOAc/hexane to afford the desired product IV.

15

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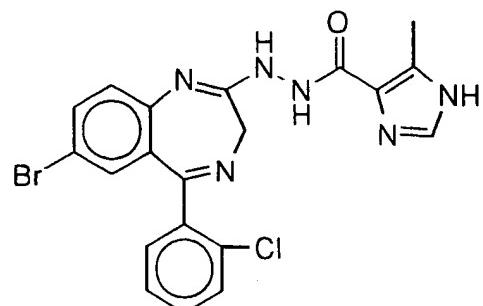
Step III Preparation of Compound VI



5 The quantity 0.056 g (0.22 mmol) of thioamide IV and
0.061 gms (0.44 mmol) of hydrazide V were heated to 80°C in a
mixture of 1.5 mL of CHCl₃ and 1.5 mL of EtOH for 16 hrs and then
allowed to cool. The residue was concentrated to dryness and
partitioned between CHCl₃ and H₂O. The water layer contained pure
10 pyrazine hydrazide starting material by TLC and was discarded. The
CHCl₃ layer, which contained some undissolved solid, was concentrated
to give a yellow solid. Trituration of this with EtOAc yielded a
colorless solid which was the desired product VI. ¹H NMR (400 MHz,
CD₃OD): 4.50 (br m, 2H), 7.14 (t, 1H), 7.20 (d, 1H), 7.32 (d, 1H),
15 7.40-7.55 (m, 6H), 8.70 (s, 1H), 8.79 (d, 1H), 9.27 (s, 1H)

- 27 -

EXAMPLE 2
Preparation of Compound VII



VII

5

Compound VII is synthesized according to Vejdelek *et al.*, Collect. Czech. Chem. Commun. 53, 132 (1988).

10 EXAMPLE 3
 HIV Integrase Assay: Substrate Cleavage

An assay for trimming of 3' end of HIV long terminal repeat terminus by HIV-1 integrase was conducted according to LaFemina, E.R. *et al.*, J. Virol. 10, 5624 (1991), herein incorporated by reference for these purposes. To assay inhibition of HIV integrase substrate cleavage, the reaction was conducted with inhibitor having various concentrations in the range of 0.1 to 100 μ M. Results follow:

	<u>Compound</u>	<u>IC₅₀</u>
	VI	2 μ M
20	VII	5 μ M.

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EXAMPLE 4

Assay for Inhibition of Strand Transfer by HIV Integrase

Inhibition of strand transfer was conducted according to Hazuda, D. J. *et al.* Nucleic Acids Res., 22, 1121 (1994), hereby 5 incorporated by reference for these purposes.

Results of the assay follow:

	<u>Compound</u>	<u>IC50</u>
10	VI	2-3 μ M
	VII	5 μ M

EXAMPLE 5

Assay for Assembly of HIV-1 Integrase as Catalytically Active Complex

Inhibition of assembly of HIV-1 Integrase was conducted 15 according to Wolfe, A.L. *et al.*, J. Virol. 70, 1424 (1996), herein incorporated by reference for these purposes.

Results of the assay follow

	<u>Compound</u>	<u>IC50</u>
20	VI	5 μ M
	VII	10 μ M

EXAMPLE 6

Oral Composition

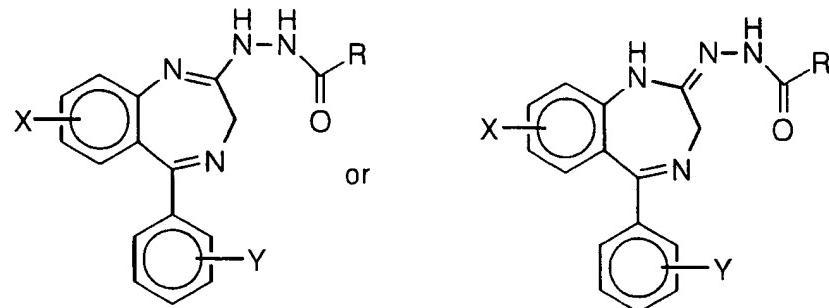
25 As a specific embodiment of an oral composition of a compound of this invention, 50 mg of a compound of the present invention is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

30 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

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WHAT IS CLAIMED IS:

1. A compound of the formula:



5

wherein:

X and Y are independently H, Cl, Br or F;

10 R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4 alkoxy, halo, nitro, phenyl or halophenyl,

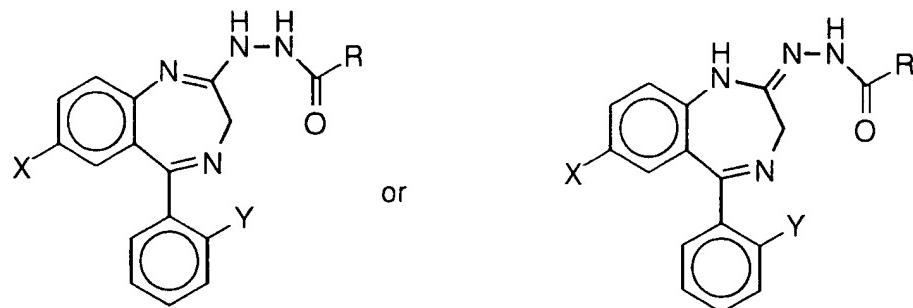
provided that:

when R is 5-methyl-4-imidazolyl, X is H or F;

15

or pharmaceutically acceptable salts thereof.

2. The compound according to Claim 1, of the formula;



20

- 30 -

wherein:

X and Y are independently H, Cl or Br;

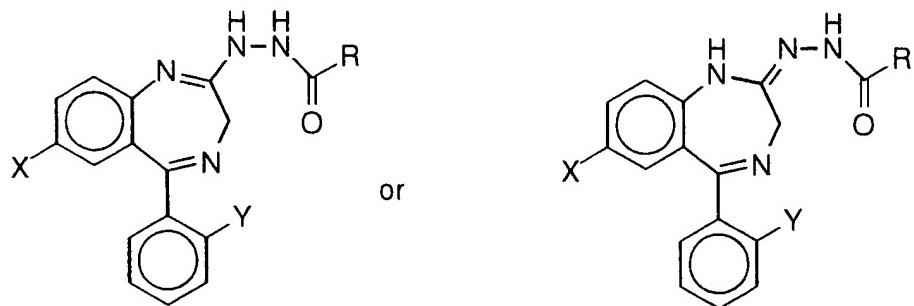
5 R is aryl or heterocycle, either of which is unsubstituted or substituted with C₁-4 alkyl, or C₁-4 alkoxy;

provided that:

when R is 5-methyl-4-imidazolyl, X is H;

10 or pharmaceutically acceptable salts thereof.

3. The compound according to Claim 1, of the formula:

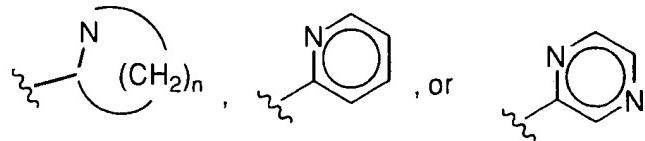


15

wherein:

X and Y are independently H, Cl, or Br;

20 R is



wherein: R is unsubstituted or substituted with one or two of:

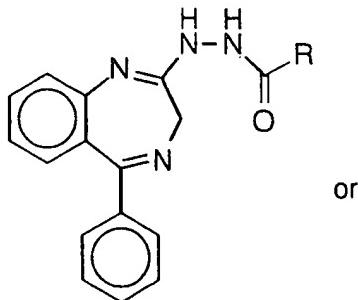
- 31 -

C₁-4 alkyl;
nitro;
C₁-4 alkoxy; or
halo-C₁-4 alkyl,

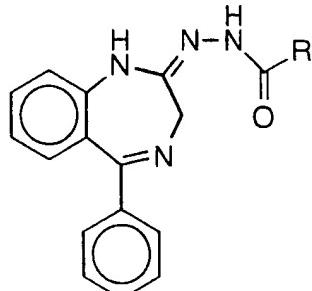
5 n is 3 to 6,

or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1, of the formula:



or



10

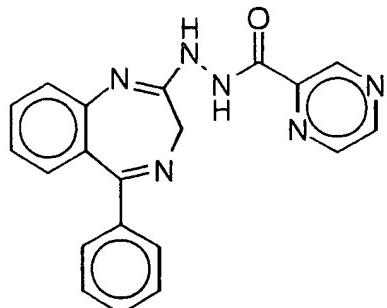
wherein:

R is aryl, pyrazinyl, pyridyl, imidazolyl, pyrimidinyl, quinolinyl, any of which R substituents are unsubstituted or substituted with C₁-4 alkyl,

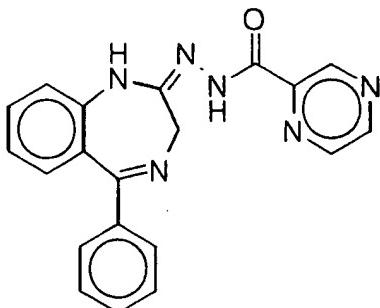
15

or pharmaceutically acceptable salts thereof.

5. The compound according to Claim 1 selected from:



and

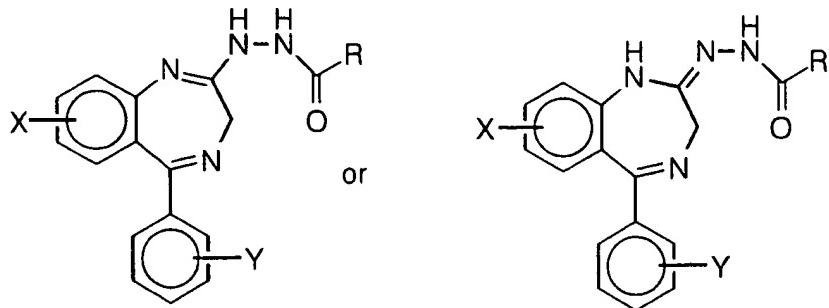


20

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or a pharmaceutically acceptable salt thereof.

6. A method of inhibiting HIV integrase, comprising
administering to a mammal an effective amount of a compound of
5 the formula:



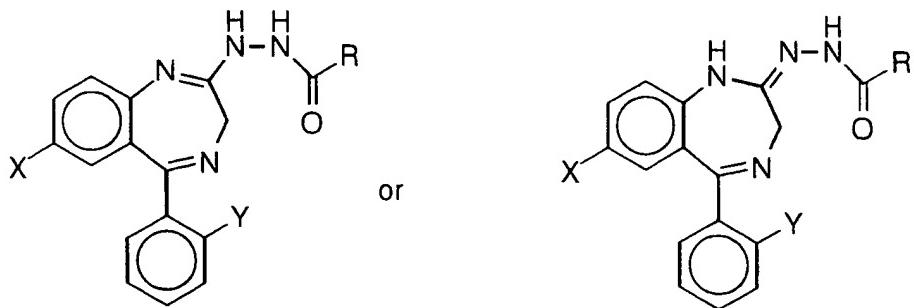
wherein:

X and Y are independently H, Cl, Br or F;

10 R is aryl or heterocycle, either of which is unsubstituted or
substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4
alkoxy, halo, nitro, phenyl or halophenyl,

15 or pharmaceutically acceptable salts thereof.

7. The method of inhibiting HIV integrase according
to Claim 6 comprising administering to the mammal an effective
amount of a compound of the formula:



20

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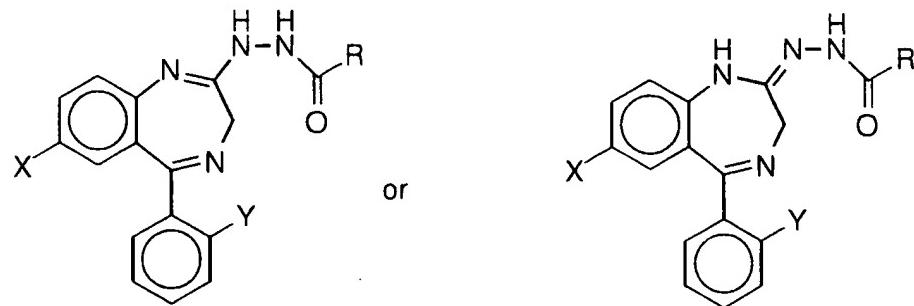
wherein:

X and Y are independently H, Cl or Br;

5 R is aryl or heterocycle, either of which is unsubstituted or substituted with C₁-4 alkyl, or C₁-4 alkoxy,

or pharmaceutically acceptable salts thereof.

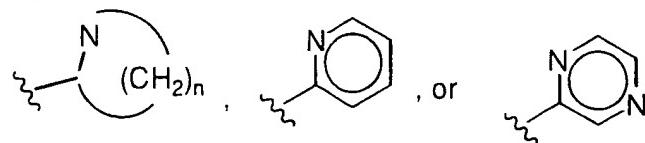
10 8. The method of inhibiting HIV integrase according to Claim 6 comprising administering to the mammal an effective amount of a compound of the formula:



15 wherein:

X and Y are independently H, Cl, or Br;

R is



20 wherein:

R is unsubstituted or substituted with one or more of C₁-4 alkyl; nitro; C₁-4 alkoxy or halo-C₁-4 alkyl,

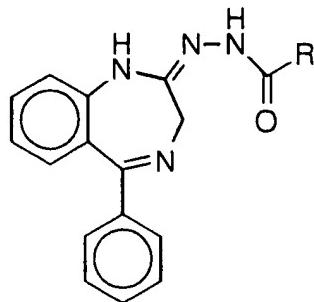
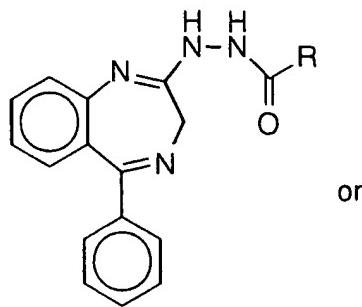
n is 3 to 6,

25

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or a pharmaceutically acceptable salt thereof.

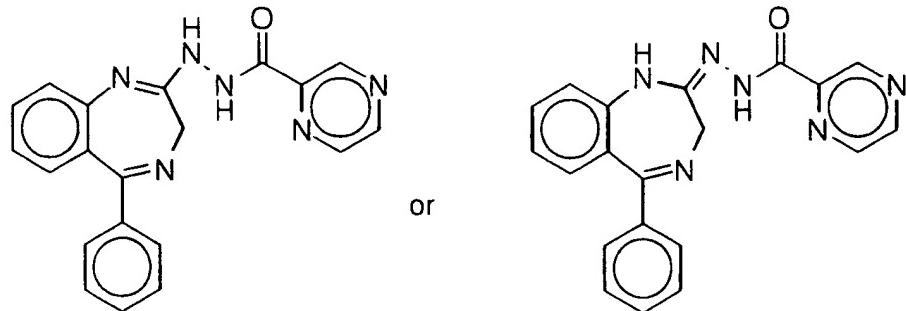
9. The method of inhibiting HIV integrase according to Claim 6 comprising administering to the mammal an effective amount of a compound of the formula:



- 10 R is aryl, pyrazinyl, pyridyl, imidazolyl, pyrimidinyl, quinolinyl, any of which R substituents are unsubstituted or substituted with C1-4 alkyl,

or a pharmaceutically acceptable salt thereof.

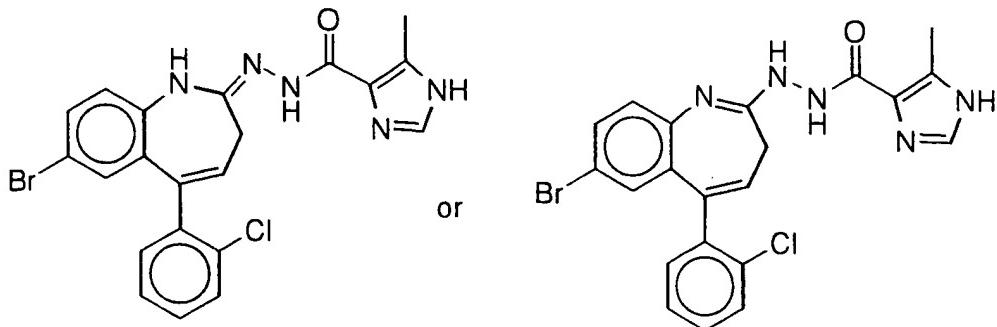
- 15 10. The method of inhibiting HIV integrase according to Claim 6 comprising administering to the mammal an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof.

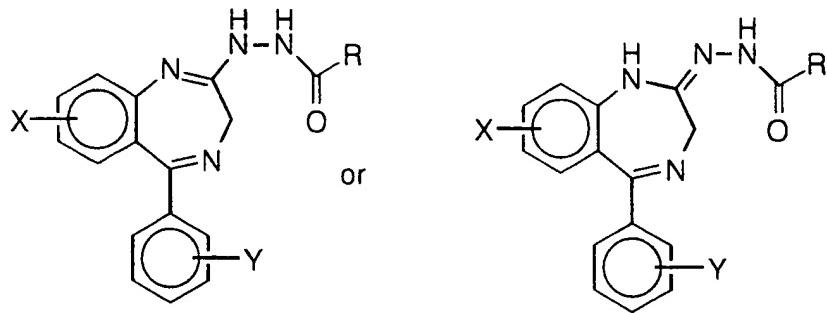
- 35 -

11. The method of inhibiting HIV integrase according to Claim 6 comprising administering to the mammal an effective amount of a compound of the formula:



5 or a pharmaceutically acceptable salt thereof.

12. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC, in a mammalian subject in need thereof, comprising administering to a
10 mammal an effective amount of a compound of the formula:



wherein:

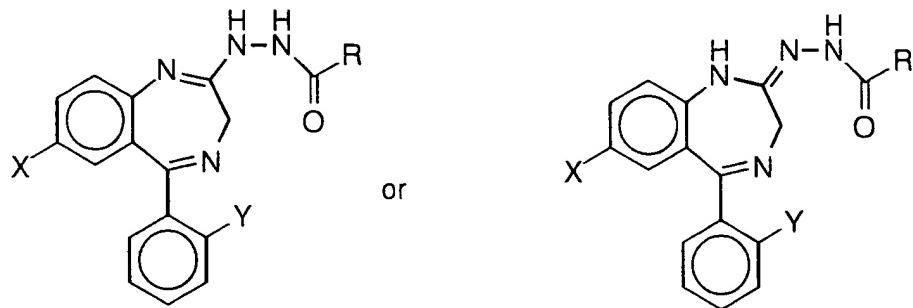
X and Y are independently H, Cl, Br or F;

15 R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4 alkoxy, halo, nitro, phenyl or halophenyl,

or a pharmaceutically acceptable salt thereof.

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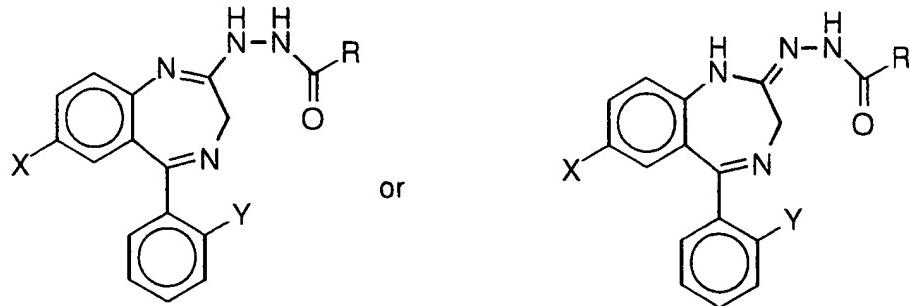
13. The method according to Claim 12, of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC in a mammalian subject in need thereof, comprising
5 administering to the mammal an effective amount of a compound of the formula:



wherein:

- X and Y are independently H, Cl or Br;
10 R is aryl or heterocycle, either of which is unsubstituted or substituted with C₁-4 alkyl, or C₁-4 alkoxy;
or pharmaceutically acceptable salts thereof.

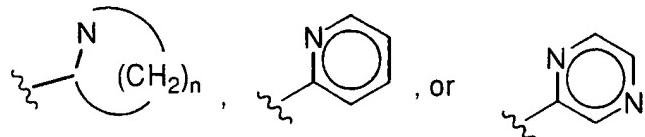
- 15 14. The method according to Claim 12, of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC in a mammalian subject in need thereof, comprising
administering to the mammal an effective amount of a compound of
20 the formula:



wherein:

X and Y are independently H, Cl, or Br;

5 R is



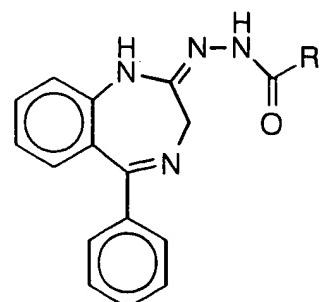
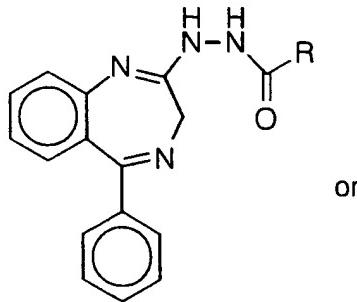
wherein R is unsubstituted or substituted with one or more of C₁-4 alkyl; nitro; C₁-4 alkoxy or halo-C₁-4 alkyl;

10 n is 3 to 6;

or a pharmaceutically acceptable salt thereof.

15. The method according to Claim 12, of preventing
infection of HIV, or of treating infection by HIV or of treating AIDS
or ARC in a mammalian subject in need thereof, comprising
administering to the mammal an effective amount of a compound of
the formula:

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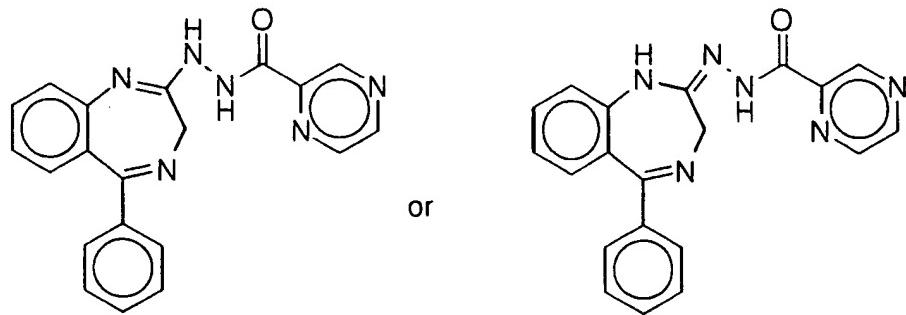


wherein:

5 R is aryl, pyrazinyl, pyridyl, imidazolyl, pyrimidinyl, quinolinyl,
any of which R substituents are unsubstituted or substituted
with C1-4 alkyl,

or a pharmaceutically acceptable salt thereof.

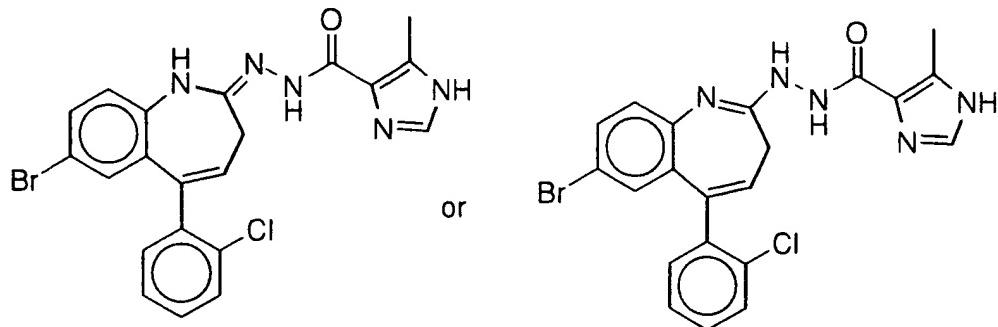
10 16. The method according to Claim 12, of preventing
infection of HIV, or of treating infection by HIV or of treating AIDS
or ARC in a mammalian subject in need thereof, comprising
administering to the mammal an effective amount of a compound of
the formula:



15 or pharmaceutically acceptable salt thereof.

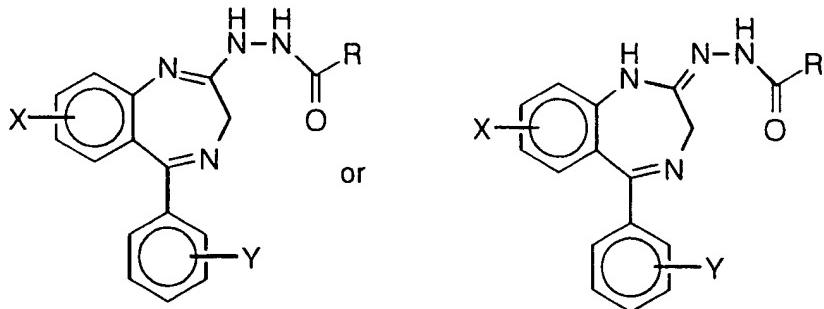
- 39 -

17. The method according to Claim 12, of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC in a mammalian subject in need thereof, comprising administering to the mammal an effective amount of a compound of
5 the formula:



or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition useful for
10 inhibiting HIV integrase, comprising a therapeutically effective amount of a compound of the formula:



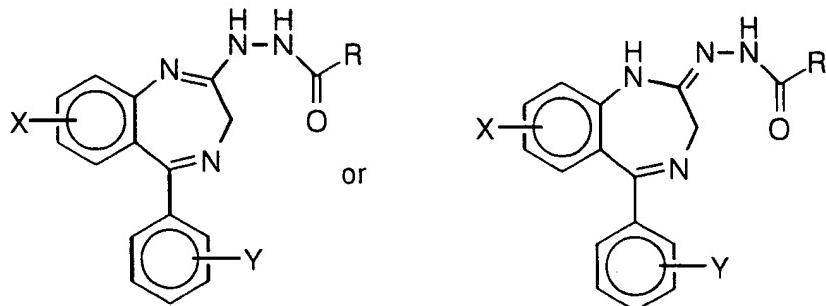
wherein:

15 X and Y are independently H, Cl, Br or F;
R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁₋₄ alkyl, phenoxy, C₁₋₄ alkoxy, halo, nitro, phenyl or halophenyl,
or a pharmaceutically acceptable salt thereof; and

- 40 -

a pharmaceutically acceptable carrier.

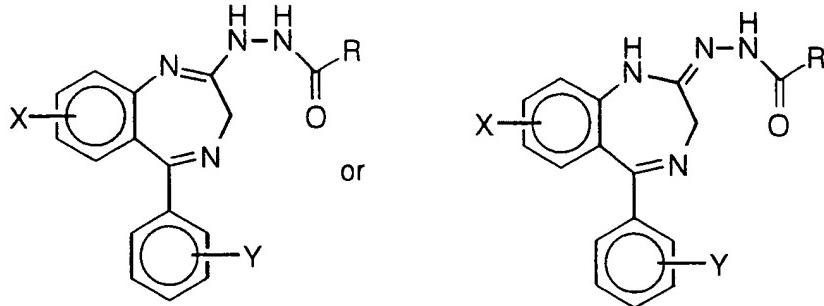
19. A pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS or
5 ARC, comprising an effective amount of a compound of the formula:



wherein:

X and Y are independently H, Cl, Br or F;
10 R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C1-4 alkyl, phenoxy, C1-4 alkoxy, halo, nitro, phenyl or halophenyl; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

15 20. A pharmaceutical composition made by combining a pharmaceutically acceptable carrier and a compound of the formula:

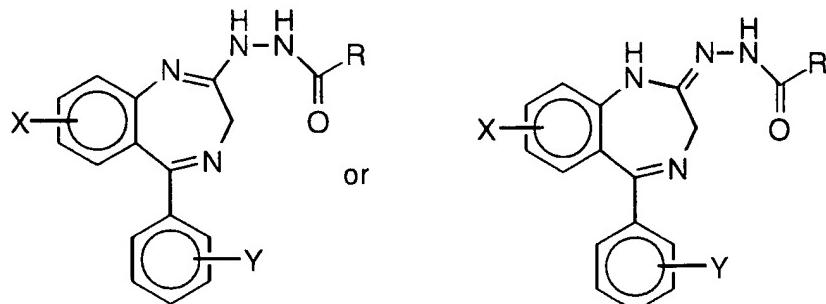


20 wherein:

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X and Y are independently H, Cl, Br or F;
R is aryl or heterocycle, either of which is unsubstituted or
substituted with amino, azido, C₁-4 alkyl, phenoxy,
C₁-4 alkoxy, halo, nitro, phenyl or halophenyl,
5 or a pharmaceutically acceptable salt thereof.

21. A process for making a composition comprising:
combining a pharmaceutically acceptable carrier and a compound of
the formula:



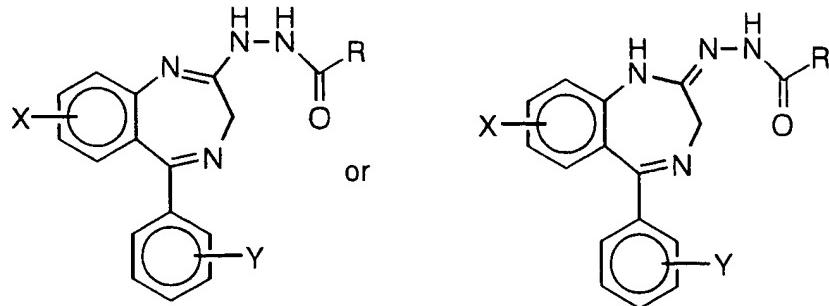
10

wherein:

X and Y are independently H, Cl, Br or F;
R is aryl or heterocycle, either of which is unsubstituted or
15 substituted with amino, azido, C₁-4 alkyl, phenoxy,
C₁-4 alkoxy, halo, nitro, phenyl or halophenyl,
or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a
20 therapeutically effective amount of a compound of the formula:

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wherein:

X and Y are independently H, Cl, Br or F;

5 R is aryl or heterocycle, either of which is unsubstituted or substituted with amino, azido, C₁-4 alkyl, phenoxy, C₁-4 alkoxy, halo, nitro, phenyl or halophenyl, or a pharmaceutically acceptable salt thereof;

in combination with a therapeutically effective amount of an AIDS
10 treatment agent selected from:

- (1) an AIDS antiviral agent,
- (2) an anti-infective agent, and
- (3) an immunomodulator.

15 23. The composition of Claim 23 wherein the antiviral agent is an HIV protease inhibitor.

24. The composition of Claim 24 wherein the HIV protease inhibitor is N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19230

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/55
US CL : 540/572; 514/221

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/572; 514/221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - A	US 4,102,881 A (TAWADA et al.) 25 July 1978, column 1, lines 7-22.	1-2, 18-21 ---
		3-17, 22-24
X - A	US 4,820,834 A (EVANS et al.) 11 April 1989, see entire document.	1-2, 18-21 ---
		3-17, 22-24
X - Y - A	VEJDELEK, Z. et al. Potential anxiolytics and hypnotics: 1-	1-2, 18-21 ---
	(alkanesulfonamidoalkyl)-6-aryl-8-halogeno-s-triazolo[4,3-a]-1,4-	
	benzodiazepines and related compounds. Collection Czechoslovak	
	Chem. Commun. 1988, Vol. 53 No. 1, pages 132-44, see entire	
	document.	3-5 ---
		6-17, 19-22

1

Further documents are listed in the continuation of Box C.

1

See patent family annex.

- | | | | |
|-----|---|-----|--|
| • | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | | |
| "B" | earlier document published on or after the international filing date | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
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